**RESPONSE**

The examiner states in the Office Action Summary that claims numbered 6, 7, 9, 12, 13, 16 and 28 are pending in the application; claims numbered 6, 7, 9, 12, 13, 16 and 28 are rejected; and claims numbered 29-31 are objected to. Applicant notes claims numbered 6, 7, 9, 12, 13, 16 and 28-31 are pending.

(2) The examiner has rejected claims numbered 6, 7, 9, 12, 13, 16 and 28 under 35 U.S.C. §103(a)) as being unpatentable over Lohray et al. (WO 97/41097).

The examiner states:

> Lohray et at. teaches at page 35, example, applicants' composition in a tablet form. Lohray et al. at page 34, lines 27-29, page 35, example, and page 7, lines 13-14, teach pharmaceutical composition containing applicants' active agent in tablet, capsule, or powder form, in combination with the pharmaceutically acceptable excipient set forth in claim 6, and flavourants, sweeteners set forth in claim 16, and other media normally employed in preparing such compositions. Lohray et at. teach that the above composition typically contains from I to 20% by weight of active compound, and the reminder of the composition being pharmaceutically acceptable carrier, diluents or solvents. (page 35, lines 1-3).
>
> Lohray et at. do not expressly teach the low water content comprising anhydrous lactose and specific cellulose set forth in claim 6 and proportions of excipients set forth in claim 9.
>
> It would have been obvious to one of ordinary skill in the art to modify Lohray composition to employ any form of lactose (e.g. anhydrous lactose) because Lohray et al. teach the composition comprising lactose in general. One would have been motivated to employ any form of lactose as taught by Lohray to provide a pharmaceutical composition containing the active agent for the effective treatment of diabetics because lactose as utilized in Lohray composition encompasses any lactose form including anhydrous lactose as claimed by the Applicants. The proportions of active agents to be used set forth in claim 9 and specified cellulose set forth in claim 6 are deemed obvious because it is within the knowledge of the skilled pharmacologist to optimize the range of amounts of active agents and the excipients to be utilized. Moreover, Lohray et at. teach the ranges of 1-20% as being an active compound and the remainder of the composition being pharmaceutically acceptable carriers, diluents or solvents. One of ordinary skill in the art would optimize this range of excipients within the range of about 20-80% as taught by Lohray et al. Further, Lohray et al. utilize one of cellulose derivative (e.g. carboxymethyl cellulose) as useful excipient and have a viable utility as an excipient which is so closely related to microcrystalline cellulose utilized claimed by the Applicants and it is to be chemically obvious there form (cellulose derivatives) in the absence of any unobvious or unexpected properties especially since one of ordinary skill in the art would expect that compounds so closely related chemically would have the same or essentially the same properties.

Applicant respectfully traverses the examiner's rejection. Lohray et al. provides no suggestion to the skilled artisan that the low-water content compositions particular to the present invention would provide a dramatic improvement to the stability of the composition as compared to the compositions of Lohray et al.

Applicant has compared compositions of the present claims with the compositions suggested by Lohray et al. The following compositions were prepared and tested for stability over a three-month period.

| Formulation | 1 | 2 | 3 |
|---|---|---|---|
| Content of formulation (mg/tablet) | Active Ingredient AI*: 10.96 mg<br>Microcrystalline Cellulose: 80 mg<br>Lactose DCL 21: 289 mg<br>Magnesium stearate: 2 mg<br>Talc: 18 mg<br>Total mass: 400 mg | Active Ingredient AI*: 10.96 mg<br>Maize starch 35 mg<br>Lactose 110 mg<br>Carboxymethyl cellulose 44 mg<br>Magnesium stearate: 1 mg<br>Total mass: 200 mg | Active Ingredient AI*: 10.96 mg<br>Maize starch 45 mg<br>Lactose: 50 mg<br>Calcium phosphate: 90 mg<br>Polyvinyl pyrrolidinone (Kollidon K 30): 3.5 mg<br>Magnesium stearate: 1.5 mg<br>Total mass: 200 mg |
| Descriptions of formulations | Corresponds to example 1 in the present application with respect to content, except for a lower content of active ingredient. The tablets were prepared by direct compression. | Corresponds to example (a), page 31 in WO 97/41097. Tablets were prepared by wet granulation. | Corresponds to example (b), page 35 in WO 97/41097. Tablets were prepared by wet granulation. |

* AI (active ingredient) is 5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiazolidine-2,4-dione, potassium salt. The tablets of formulation 2 and 3 were prepared by wet granulation as in examples (a) and (b) in WO 97/41097, page 35. The tablets of formulation 1 were prepared by direct compression as in example 1 of the present application.

The data in Table 1 (below) shows the analytical data obtained for the three formulations during storage. Data for the remaining AI (Assay) and for the impurities are given.

Table 1: Stability results (assay and degradation products) at 40°C/75% relative humidity, open container:

| Months of storage | Formulation 1 | | | Formulation 2 | | | Formulation 3 | | |
|---|---|---|---|---|---|---|---|---|---|
| | Assay mg/tab | Degradation products | | Assay mg/tab | Degradation products | | Assay mg/tab | Degradation Products | |
| | | Largest single % | Sum % | | Largest single % | Sum % | | Largest single % | Sum % |
| 0 | 9.73 | 0.20 | 0.63 | 8.83 | 0.22 | 0.70 | 9.11 | 0.23 | 0.77 |
| 1 | - | - | - | 6.02 | 4.02 | 8.78 | 8.28 | 2.44 | 7.05 |
| 3 | 9.27 | 3.67 | 4.83 | 7.99 | 6.02 | 13.83 | 8.25 | 3.94 | 10.99 |
| 6 | 8.79 | 1.51 | 4.37 | NA | NA | NA | NA | NA | NA |

It is clear from the data in the table that the stability of formula 1 is superior to that of formulations 2 and 3. After three months, the sum of degradation products for formulations 2 and 3 is 2.3 – 2.9 times that of the sum of degradation products for formulation 1. The six month data for formulations 2 and 3 is not available yet. However the fact that the sum of the degradation products for formulation 1 appears to have leveled out suggests that the sum of degradation products after six months for formulation 2 and 3 will be at least 2.3 – 2.9 times that of the sum of degradation products for formulation 1.

The above data show that improved stability can be obtained for compositions comprising 5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiazolidine-2,4-dione or pharmaceutically acceptable salts thereof, and low-water content lactose, microcrystalline cellulose and/or talc. Furthermore, there is no suggestion in Lohray et al. to the skilled artisan that the compositions particular to the present invention would provide such a drastic improvement to the stability of the composition as compared to the compositions of Lohray et al.

Applicant respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a), and the objection to the claims dependent on the rejected base claim.

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Applicant believes the claims are in condition for allowance. The examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application. Applicant respectfully requests that a timely Notice of Allowance be issued in this case.

Respectfully submitted,

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Rosemarie R. Wilk-Orescan
Registration Number 45,220
Novo Nordisk Inc.
100 College Road West
Princeton, NJ 08540
(609) 987-5969

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